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Visceral fat and metabolic inflammation: The portal theory revisited

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Abbreviations

FFA	free fatty acid
RBP4	retinol-binding protein 4
IL-1β	interleukin 1β
IL-6	interleukin-6
IL-8	interleukin-8 (mouse homologue KC)
TNF-α	tumor necrosis factor-α
MCP-1	monocyte chemoattractant protein 1
UCP1	uncoupling protein 1
SOCS3	suppressor of cytokine signaling 3

Abstract

Abdominal (central) obesity strongly correlates with (hepatic) insulin resistance and type 2 diabetes. Among several hypotheses that have been formulated the 'portal theory' proposes that the liver is directly exposed to increasing amounts of free fatty acids and pro-inflammatory factors released from visceral fat into the portal vein of obese patients, promoting the development of hepatic insulin resistance and liver steatosis. Thus, visceral obesity may be particularly hazardous in the pathogenesis of insulin resistance and type 2 diabetes. Herein, we will critically review existing evidence for a potential contribution of portally-drained free fatty acids and/or cytokines in the development of hepatic insulin resistance.

Introduction

Obesity results from a longstanding dys-balance of caloric intake exceeding energy expenditure, and is associated with an increased number and size of white adipocytes storing the excessive energy in the form of triglycerides. In recent years it has become evident that adipose tissue has, in addition to its major metabolic tasks, endocrine functions mediated by secretion of different adipokines, cytokines and fat-derived metabolites such as free fatty acids (FFAs). These in turn may act locally, i.e. in an autocrine/paracrine manner, or affect the central nervous system, skeletal muscle, the liver and pancreatic β-cells to regulate food intake, energy expenditure, and glucose homeostasis (1, 2). This endocrine function of adipose tissue contributes to the pathogenesis of detrimental consequences of obesity, such as insulin resistance and type 2 diabetes (2, 3). However, not all obese individuals are insulin resistant and diabetic (4), and conversely, conditions with pathologically diminished fat mass (lipodystrophies) are also associated with insulin resistance (5).

Jean Vague was the first to notice that the distribution of fat may influence the predisposition to metabolic diseases (6). Individuals with central obesity (also known as android type or "apple-shaped" obesity) accumulate fat mainly in intra-abdominal and upper thoracic deposits. Numerous epidemiological studies have reported a close association between central obesity, insulin resistance and a cluster of different metabolic diseases (7-13). In contrast, individuals with peripheral obesity (also known as gynoid type or "pear-shaped" obesity) have a predominantly subcutaneous accumulation of adipose tissue in the femoral-gluteal region. Individuals with such type of fat distribution seem to be less susceptible for metabolic complications (14-16) or they may be even protected from insulin resistance and dyslipidaemia (17-19). On the other hand, individuals with a decreased energy storage capacity in peripheral subcutaneous adipose tissue deposit increasing amounts of fat in liver, skeletal muscle and heart and, thus, may be prone to develop insulin resistance and type 2 diabetes as suggested by the "ectopic fat hypothesis" (20).

All these observations may suggest that it is not merely the increase in adipose tissue mass *per se* that alters the function of target organs in obesity. Rather, accompanying alterations in the endocrine and metabolic functions as well as the location of adipose tissue may contribute to insulin resistance and diabetes. However, due to inaccuracy in body fat depot measurements and biological variation in fat depot characteristics, the causal relationship of central obesity and (hepatic) insulin resistance is only poorly understood and the impact of different fat depots on the development of metabolic complications is still open to controversy (21, 22). In particular, it is unclear whether the different biological nature of visceral fat is driving the apparent stronger association between visceral fat and morbidity or whether it is the mere drainage to the liver as suggested by the 'portal theory'. The present review will discuss current evidence in support of the 'portal theory'.

Functional differences between different fat depots

Functional analyses have identified differences between various fat depots (23). For example, basal lipolysis rates are higher in adipocytes isolated from omental and mesenteric adipose tissue compared to adipocytes isolated from subcutaneous fat in humans (24-26). Furthermore, the stimulatory effect of catecholamines on lipolysis is stronger while the suppressive effect of insulin is weaker in omental compared to subcutaneous adipose tissue (26, 27). Mechanistically, such observation may be partly explained by the preponderance of stimulatory β-adrenoceptors over antilipolytic α-adrenoceptors and the lower insulin receptor affinity (i.e. its ability to bind insulin) of mesenteric/omental adipocytes (25, 27). Consequently, circulating FFA concentration may be higher in the portal circulation as compared to systemic circulation as was shown in lean mice (28). In addition, evidence exists that not only lipolysis, but also lipogenesis varies between fat depots, indicating that varying rates of lipid synthesis contributes to the diverse nature of the different fat depots (29-31).

There is evidence that adipocytokines may be differently expressed in and secreted from different adipose depots. For example, gene expression and secretion rate of leptin, which regulates food intake and energy expenditure, are two to three times higher in subcutaneous compared to omental adipose tissue, indicating that subcutaneous adipose tissue is the more important source of adipose-derived leptin (32, 33). In contrast, secretion of adiponectin, which was found to have insulin-sensitizing and anti-inflammatory properties (34-36), is higher from isolated omental compared to isolated subcutaneous adipocytes (37) albeit the overall contribution from the latter is still higher given its mass. Moreover, its plasma levels decrease in parallel with the progression of obesity and type 2 diabetes (38). Interestingly, adiponectin secretion from omental adipocytes was reduced to a greater degree in more obese individuals, which may explain the decline in plasma adiponectin levels observed in obesity (37). Retinol-binding protein (RBP) 4 and resistin are both associated with insulin resistance and type 2 diabetes (39, 40). Importantly administration of recombinant resistin rapidly induced severe hepatic but not peripheral insulin resistance in rats (41). Whereas mRNA expression of resistin appears to be similar from omental and abdominal subcutaneous fat (42), a higher expression rate has been reported for RBP4 in omental compared to subcutaneous fat in human subjects (43). In addition, several pro-inflammatory factors such as interleukin 1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8; mouse homologue KC), tumor necrosis factor-α (TNF-α) and monocyte chemoattractant protein 1 (MCP-1) are secreted from adipocytes (as well as non-adipocyte cells such as macrophages), thus contributing to the chronic low-grade inflammatory state often observed in obesity (44). The impact of these cytokines on insulin resistance as well as their depot-specific differences in expression and secretion will be discussed below. Collectively, expression and secretion pattern of various adipocytokines differs between fat depots and hence, given their proposed role in the development of insulin resistance, may partly explain the different impact of central versus peripheral obesity on insulin sensitivity and glucose metabolism.

Compatible with these functional differences, a multitude of developmental and adipogenic genes are differentially expressed in visceral and subcutaneous adipose tissue both in humans and rodents (45-48). Of note, isolated and cultured preadipocytes maintained their unique gene expression pattern indicating its cell specificity and its independency of tissue environment (49).

Recently, it was proposed that two different types of adipocytes may exist within white adipose tissue: the “genuine” white adipocytes and the brown-in-white “brite” adipocytes. The latter express uncoupling protein 1 (UCP1), a classical marker for brown adipocytes, but otherwise do not possess the full molecular characteristics of brown adipocytes (50). Interestingly, distribution of such “brite” adipocytes differs considerably between different white adipose depots in mice: it is higher in inguinal fat depots and low in perigonadal and mesenteric fat tissue (51). It is plausible that the distinct “brite” adipocyte content of different depots will impact on their function, e.g. their low content may contribute to the increased lipid release of mesenteric adipose tissue. Presently, it is not clear whether ‘brite’ adipocytes do exist in human white adipose depots and whether these cells could be functionally recruited to prevent or treat obesity (52).

Intra-abdominal adipose tissue comprises different fat depots

Intra-abdominal fat constitutes only about 10% of total body fat (53) and includes omental, mesenteric, perirenal and perigonadal fat depots (the latter is only found in rodents, though). Visceral adipose tissue refers to the fat depots surrounding the internal organs (viscera) and is often used synonymously for intra-abdominal fat. However, such generalization may be misleading since not all fat depots located intra-abdominally surround visceral organs. For example, the unique perigonadal fat depot, which has no human correspondent (22), is attached to the testis/epididymis (therefore also known as epididymidal fat tissue) in males and to the fallopian tube in females, which are not considered to be part of the visceral organs. Thus, perigonadal adipose tissue does not comprise visceral adipose tissue in its proper sense even

though it is often categorized as such (54-57). In agreement with such notion, mRNA expression pattern differ between perigonadal and mesenteric adipocytes (51). Additionally, functional disparities appear to occur as we recently reported differences in lipolysis between perigonadal and mesenteric adipocytes (28).

Moreover, venous drainage differs between intra-abdominal fat depots: Omental (which is insignificant in rodents) and mesenteric fat depots are drained by the portal vein whereas other depots such as the perirenal, the retroperitoneal and the afore-mentioned perigonadal adipose tissue are drained systemically, i.e. by the inferior and superior caval veins (Fig. 1). Thus, the liver is directly exposed to cytokines and FFAs released by portally-drained adipose depots, whereas these factors and metabolites circumvent the liver when released systemically and, thus, reach the liver only after being diluted in the systemic circulation. It was therefore hypothesized in what is known as the 'portal theory' that the exaggerated release of FFAs and pro-inflammatory cytokines from visceral fat are directly delivered to the liver via portal vein, promoting the development of hepatic insulin resistance and hepatic steatosis in obese individuals (25, 58, 59).

Thus, there are different intra-abdominal fat depots that have distinguished functional and anatomic properties. Such notion should be kept in mind when analyzing function and metabolism of different intra-abdominal depots in rodents and humans.

Adipose tissue inflammation as a hallmark of obesity

In obesity, adipose tissue expansion is associated with local infiltration of different types of inflammatory cells (60-63). As in other non-infectious (sterile) inflammatory processes (64), "chronic" inflammatory infiltration of adipose tissue by mainly mononuclear cells seems to be preceded by a transient infiltration with circulating neutrophils, which can be found as early as three days after the initiation of high fat-feeding in mice (65). Subsequently, macrophages gradually become the quantitatively predominant inflammatory cell type infiltrating adipose

tissue (although other immune cells like T and B lymphocytes and mast cells have been reported as well (44, 62, 63, 66-68)). These cells secrete different cytokines such as IL-1β, IL-6, IL-8, TNF- α and MCP-1, which in turn alter the expression and secretion pattern of adipokines and cytokines in adipose tissue. As a consequence, insulin sensitivity is impaired locally and systemically (44, 69, 70). Accordingly, it was recently demonstrated that insulin-resistant morbidly obese individuals have a significantly higher number of macrophage infiltration in their omental adipose tissue compared to insulin-sensitive individuals (4). In this scenario, adipose tissue inflammation is suggested to play a role in the induction of adipose tissue dysfunction. Yet, an alternative scenario puts adipose tissue alterations upstream of the recruitment of inflammatory cells into fat tissue and the development of adipose tissue inflammation. A primary event in the latter proposition is increased triglyceride storage (and subsequential fat cell hypertrophy and cell death) and/or increased basal (non-stimulated) lipolysis leading to the recruitment of inflammatory cells, to changes in adipokine production, and to increased cytokine secretion from hypertrophied adipocytes. In this regard, toll-like receptors might play a pivotal role, being activated in macrophages by elevated levels of saturated FFAs (71-73). Alternatively, the latter may activate JNK via induction c-Src clustering within membrane subdomains (74) and/or via activation of double-stranded RNA-dependent protein kinase (PKR) (75). Thus, altered adipokine/cytokine secretion by adipose tissue could constitute both a cause and a consequence of adipose tissue inflammation. Taken together, adipose tissue infiltration with inflammatory cells and the resulting crosstalk with local cells such as adipocytes appear to have a major contribution to the development of obesity-induced insulin resistance and type 2 diabetes.

How is central obesity linked to (hepatic) insulin resistance?

As outlined above, there is a large body of clinical evidence suggesting a strong link between central (abdominal) fat accumulation and the development of insulin resistance and type 2 diabetes (7-13, 76). This relationship was found to be stronger than with measures of general

obesity, such as BMI (10, 77). Moreover, lifestyle intervention-induced reduction in visceral fat mass was associated with improved insulin sensitivity suggesting that intra-abdominal fat accumulation may be causatively linked to insulin resistance (78). How does visceral fat accumulation impact on (hepatic) insulin sensitivity? It was suggested that increased release of lipids from omental and mesenteric adipose tissue in obesity results in increased portal FFA concentration (58), which in turn induce hepatic insulin resistance. Indeed, chronic exposure of the liver to elevated FFAs was previously found to inhibit the action of insulin and, consequently, to stimulate gluconeogenesis (9, 25, 79-81). Accordingly, several gene transcripts involved in lipid turnover in omental fat and rate-limiting gluconeogenic enzymes in the liver were elevated in the fat-fed dog model (82). In addition, liver triglyceride content was increased and insulin receptor binding decreased. Moreover, infusion of FFAs induced peripheral and hepatic insulin resistance in humans (83, 84), whereas the lowering of FFA plasma levels enhanced insulin-induced suppression of endogenous glucose production during hyperinsulinemic-euglycemic clamps in type 2 diabetic individuals (85). Thus, FFAs appear to be an important signal controlling endogenous glucose output (86, 87) and it is conceivable that in obesity increased flux of FFA from visceral fat depots to the liver will result in hepatic insulin resistance and hepatic steatosis (58). Consequently, the 'portal theory' has initially been explained by a relative high lipolysis rate specifically in visceral adipose tissue, which increases the portal concentration of FFAs in obesity leading to hepatic insulin resistance and metabolic abnormalities. However, we recently compared lipolysis rate in mesenteric adipocytes isolated from mice fed either a standard or fat-enriched diet and we unexpectedly found that basal lipolysis was not increased in mesenteric adipocytes isolated from high fat diet-fed mice (28). In accordance, FFA concentration in portal blood did not increase in high fat diet-fed animals even though they developed (hepatic) insulin resistance and steatosis. Similarly, Frayn et al. reported that the rates of FFA delivery were downregulated with maintained systemic plasma FFA concentrations in

abdominally obese men, both in the fasted and postprandial state (88). Thus, the concept of obesity associated with elevated FFA levels may be questioned (89).

In the above mentioned study, we observed an increased release of pro-inflammatory cytokines such as IL-6 from mesenteric adipocytes of high-fat compared to standard diet fed mice (28). Accordingly, omental adipose tissue was previously reported to release two to three times more IL-6 than subcutaneous adipose tissue in obese subjects (90). Moreover, IL-6 levels were higher in portal vein compared to radial artery samples in obese individuals (91). In mice, IL-6 was previously shown to reduce insulin's ability to suppress basal endogenous glucose production during hyperinsulinemic-euglycemic clamps, indicating that IL-6 induced hepatic insulin resistance (92). Consistently, IL-6 concentration was elevated in various insulin-resistant mouse models (93) and treatment with IL-6 neutralizing antibody improved hepatic insulin sensitivity (94). Mechanistically, chronic IL-6 treatment suppresses insulin-dependent insulin receptor autophosphorylation and tyrosine phosphorylation of insulin receptor substrate 1 (IRS-1) in the liver of C57BL/6 mice (95), probably via stimulation of suppressor of cytokine signaling 3 (SOCS3). The latter suppresses insulin signaling via direct interaction with the insulin receptor (96, 97). In contrast, mice with a liver-specific deletion of the *IL-6 receptor α* gene exhibited reduced insulin sensitivity and glucose tolerance (98) suggesting that IL-6 at low concentration has permissive effects on insulin sensitivity and glucose metabolism, but at high concentration detrimental effects. Furthermore, muscle-derived IL-6 is now recognized as a major contributor to the mobilization of lipids during physical activity (99). Thus, the role of IL-6 in glucoregulatory processes may be neither exclusively beneficial nor harmful (100).

Besides IL-6 other pro-inflammatory cytokines such as IL-1β may be released in increasing amounts from visceral fat depots and contribute to hepatic insulin resistance. In obese individuals, elevated IL-1β expression and secretion was observed in visceral/omental compared to subcutaneous adipose tissue and to tissues from lean individuals (101-103). Consistently, IL-1β release in human omental fat explants positively correlated with body mass index (104). In

mice, IL-1β levels were significantly elevated in portal but not systemic blood after eight weeks of high fat diet when compared with regular chow diet (own observations and (104)). IL-1β treatment of hepatoma cell lines and primary rat hepatocytes induced insulin resistance *in vitro*. Moreover, conditioned medium from 3T3-L1 adipocytes pretreated with TNFα deteriorated insulin-signaling in Fao hepatoma cells IL-1β-dependently suggesting a potential role of adipocyte-derived IL-1β as a mediator in the perturbed cross talk between adipocytes and liver cells in response to adipose tissue inflammation (104).

In summary, increased production and release of pro-inflammatory cytokines such as IL-6 and/or IL-1β from omental and mesenteric adipocytes into the portal vein may contribute to the development of hepatic insulin resistance. Thus, the 'portal theory' may be explained as an increased release of both FFAs and/or pro-inflammatory cytokines into the portal circulation (105). Presently, further studies are needed to confirm a significant contribution of pro-inflammatory cytokines to the 'portal theory'. Moreover, it is conceivable that obesity-associated changes in the composition of the gut microbiota and the resulting release of gut-derived pro-inflammatory and bacterial factors such as endotoxin may contribute to the 'portal theory' since large parts of the small bowel are also drained into the portal vein (106).

However, the hitherto presented data are mainly correlative and do not directly prove causality between central obesity (i.e. increased portally-drained visceral adipose tissue mass) and hepatic insulin resistance/deteriorated glucose metabolism. To directly test such causal link, both lipectomy and transplantation studies were performed. Results are controversial and not all of them support the 'portal theory' as outlined below.

Direct evidence in support of the 'portal theory'

In obese individuals, omentectomy performed together with gastric banding significantly improved glucose metabolism and insulin sensitivity (107). However, since individuals with both interventions lost on average an additional nine kilograms of body mass it remains unclear

whether the observed metabolic improvement was due to the reduction in omental fat only or to the overall loss in fat mass (107, 108). In addition, two recent publications reported no additional benefit of omentectomy on insulin sensitivity in morbid obese people (109, 110). In rodents, several studies aimed to investigate the impact of lipectomy on glucose metabolism and, indeed, removal of epididymal and perirenal depots was reported to improve glucose metabolism (111, 112). However, since these depots are systemically drained, no conclusion regarding a potential detrimental effect of portally drained adipose tissue on (hepatic) insulin sensitivity can be drawn. Of interest, removal of small pieces of (portally drained) mesenteric adipose tissue improved glucose tolerance and hepatic triglyceride content in rats (113) supporting a potential role for the 'portal theory' in the pathogenesis of obesity-induced insulin resistance.

To directly test the hypothesis that portally drained visceral fat induces hepatic insulin resistance we performed fat transplantation experiments. To this end we transplanted epididymal fat depots from lean donor to healthy littermates (C57Bl6/J mice) either to systemically drained or to portally drained sites (114, 115). Only mice receiving portally drained fat transplants exhibited impaired glucose tolerance compared to sham-operated mice, whereas mice receiving systemically drained transplants revealed improved glucose tolerance. Moreover, hyperinsulinemic-euglycemic clamps revealed that insulin-induced suppression of endogenous glucose production was blunted in mice receiving portally drained fat transplants providing perhaps the most direct evidence yet supporting the 'portal theory'. In contrast to our study, two recent studies reported no changes or even improvement in glucose tolerance after epididymal or mesenteric fat transplantation into the abdominal cavity (116, 117). However, both studies provided no evidence for pure portal drainage of their fat transplants or as for the paper by Tran et al. it is assumed that fat pads were drained to both the caval as well as to the portal vein (117). Similarly, we found that mice receiving both a systemically as well as a portally drained fat transplant showed no net alteration in glucose tolerance (115). One potential explanation might be the fact that the beneficial metabolic effect of the systemically-drained fat transplant (114) was

balanced by the detrimental effect of the portal-drained transplant. Intriguingly, expression of pro-inflammatory cytokines such as IL-6 was increased in transplanted fat pads and, consequently, concentration of IL-6 was increased in portal but not systemic circulation whereas FFA levels were not altered when compared to sham-operated mice. Moreover, mice receiving portally drained fat transplants from IL-6 deficient donors no longer developed hepatic insulin resistance. Such finding strongly argues for an important role for portally mediated pro-inflammatory cytokines in the development of hepatic insulin resistance and further supports a significant role for pro-inflammatory cytokines in the 'portal theory'.

Evidence challenging the 'portal theory'

Although numerous studies have shown evidence for a major role of (portally drained) visceral adipose tissue in the development of (hepatic) insulin resistance and metabolic diseases, its predominant contribution has been questioned (22, 108, 118, 119). The most common argument raised against the 'portal theory' states that insulin-mediated glucose disposal not only correlates inversely with visceral fat, but also with abdominal subcutaneous fat mass, indicating that the systemically drained subcutaneous adipose tissue may have detrimental effects on glucose homeostasis (53, 120-122). Although correlation studies highlight a potential association, they obviously do not prove causality. Moreover, abdominal subcutaneous fat mass itself strongly correlated with intraperitoneal fat mass in asymptomatic middle-aged men with a wide range of adiposity (53). Similarly, a strong correlation was reported for asymptomatic women (118, 123). Therefore, such studies do not necessarily argue against an important role of the 'portal theory' in the pathogenesis of obesity-associated insulin resistance.

Another argument often raised against the 'portal theory' is the finding that relative low amounts of FFAs originate from visceral adipose tissue. Since it is technically difficult to measure FFAs directly in the portal vein of humans, Jensen *et al.* developed an isotope dilution technique to measure systemic and regional FFA uptake and release indirectly (124). Using such

attractive technique they were able to show that with increasing mass visceral fat depots released increasing amounts of FFAs into the portal vein, even though the relative contribution of any individual fat depot was quite variable (125). Most importantly, the relative amount of portal vein FFAs derived from visceral fat was suggested to be much less than the relative amount derived from lipolysis of subcutaneous fat. It was calculated that only approximately 5-30% of portal vein FFAs originated from visceral fat in lean as well as in obese subjects. It was therefore concluded that visceral fat is not as important as subcutaneous fat in supplying FFAs to the liver both in lean and in obese individuals (22, 108, 125). However, although the relative contribution of FFA from visceral fat to the systemic circulation is low, the direct exposure of the liver to FFAs derived from the portal vein may still have detrimental effects. In addition, the composition of FFA released from (visceral) adipose tissue may change in obesity. Furthermore, increased release of pro-inflammatory cytokines into portal circulation may play a more crucial role in the development of hepatic insulin resistance than increased FFA release as outlined above (105, 115).

Conclusions and final remarks

The 'portal theory' comprises the concept that direct exposure of the liver to increasing amounts of FFAs and/or pro-inflammatory factors released from visceral adipose tissue (and/or the gut) directly into the portal vein importantly contributes to the development of hepatic insulin resistance and hepatic steatosis (Fig. 2). Such notion is supported by the fact that omental and mesenteric adipose tissue have distinct functional properties compared to subcutaneous adipose tissue such as altered production and secretion pattern of adipocytokines in obesity. Moreover, ectopic storage of fat in tissues such as liver and skeletal muscle was proposed to play a crucial role in the development of insulin resistance and type 2 diabetes (126, 127) and, thus, in accordance with the 'portal theory' a decreased storage capacity especially of portally drained adipose tissue may oversupply the liver with lipids resulting in (ectopic) fat accumulation. We

believe that we presented herein good clinical and experimental evidence in support of the 'portal theory'. However, further studies are needed for a better and comprehensive understanding of the apparent causal link between visceral obesity and (hepatic) insulin resistance.

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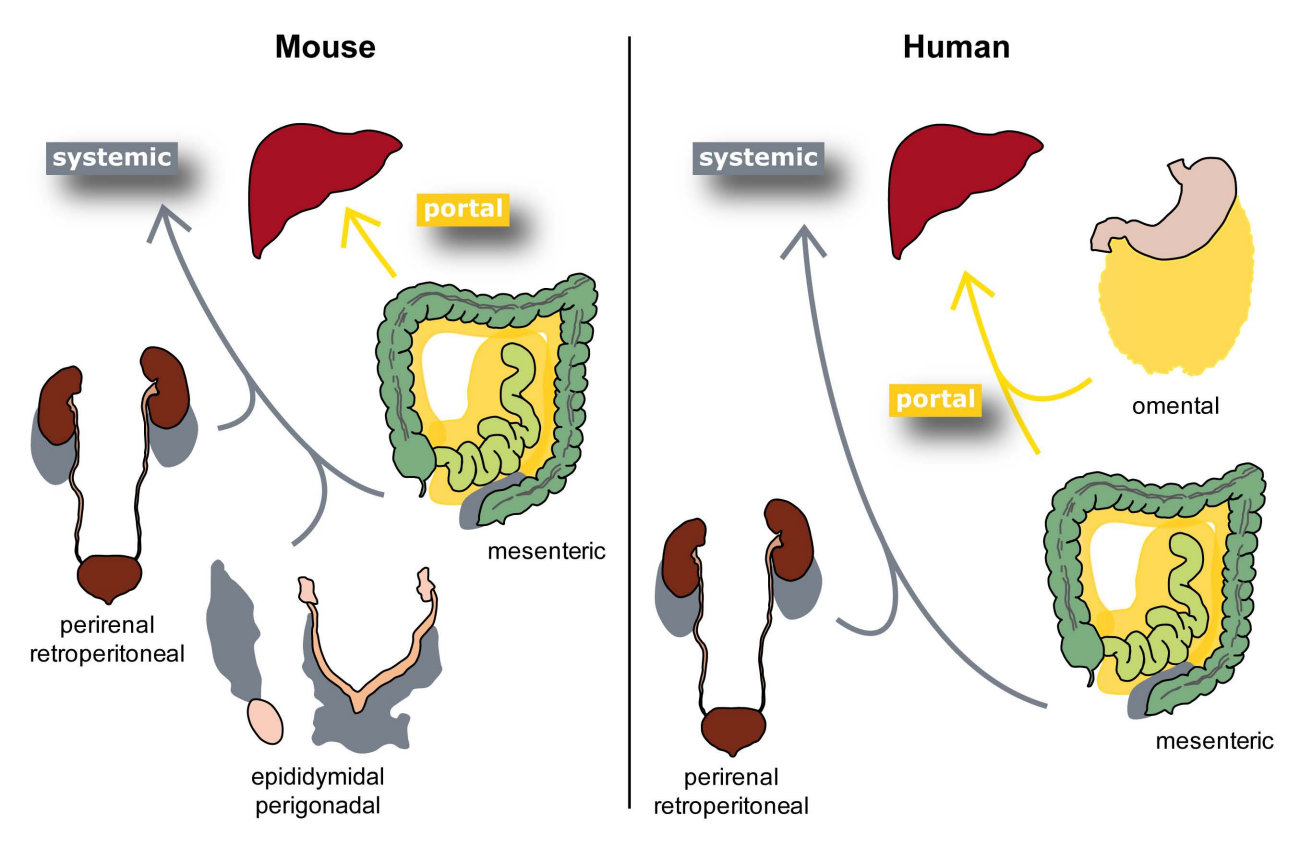
Fig. 1 Intra-abdominal adipose tissue compromises different fat depots

Venous drainage differs between intra-abdominal fat depots both in mice and humans: Omental fat, which is insignificant in rodents, is drained by the portal vein (yellow). Mesenteric adipose tissue compromises fat depots surrounding the small bowel (light green) and the colon (dark green). These fat depots are drain to the portal vein (yellow) except for the fat tissue surrounding the lowest part of the colon (rectum), which is drained to the vena cava inferior, i.e. systemically (grey). All other intra-abdominal fat depots such as the perirenal, the retroperitoneal and the perigonadal adipose tissue are drained by the inferior caval vein (systemically). Yellow stained fat depots: drained to the portal vein; grey stained fat depots: drained to the vena cava inferior.

Fig. 2 Proposed mechanisms for visceral obesity-induced insulin resistance ('portal theory')

Individuals with central obesity accumulate fat mainly in intra-abdominal deposits, i.e. in mesenteric and/or omental adipose tissue. The concomitant increased release of free fatty acids and/or pro-inflammatory factors from these depots are drained via the portal vein directly to the liver. Additionally, increased release of gut-derived pro-inflammatory and bacterial factors such as endotoxin might contribute to the 'portal theory' since large parts of the small bowel are also drained into the portal vein. Hepatic exposure to these factors will result in the development of hepatic insulin resistance, steatosis and inflammation.


Mouse
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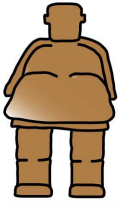
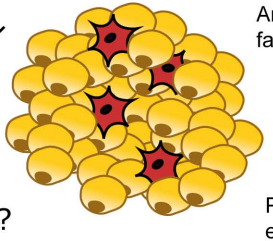


Central obesity

Mesenteric / omental adipose tissue

Adiponectin ↓

Anti-inflammatory factors ↓



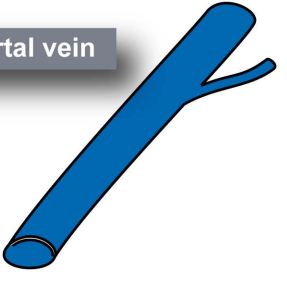
Free fatty acids ↑ ?

↑ Gene transcripts involved in lipid turnover and gluconeogenesis

Insulin resistance
Steatosis
Inflammation

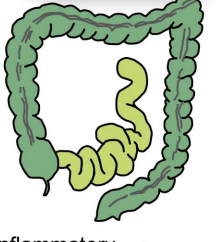
Liver

Portal vein



Pro-inflammatory factors e.g. IL-6, IL-1β ↑

Intestine



Bacterial factors e.g. endotoxins ↑

Pro-inflammatory factors ↑